In This Issue

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T-CELL RECEPTOR–ANTIGEN INTERACTION DEFINED IN AUTOIMMUNE VITILIGO

Vitiligo is a common disorder of cutaneous depigmentation, which, though acquired, has a definite genetic predisposition. While the endpoint of vitiligo is clearly loss of melanocytes, the pathomechanism of vitiligo has been a subject of longstanding debate. Textbooks present the neural hypothesis, the self-destruct hypothesis, and the autoimmune hypothesis as possible explanations for vitiligo; these mechanisms may not be mutually exclusive. It is clear that skin-homing T-cells can be found at the margins of depigmented vitiligo lesions. Autoimmune mechanisms for attacking the melanocyte include influx of skin-homing autoreactive T-cells, aided by cytotoxic antibodies, complement factors, and nitric oxide (NO). These mechanisms may be further abetted by toxic by-products of melanin biochemistry. In this issue, Mantovani *et al* (p. 308) present some exciting new insights into the autoimmune hypothesis of vitiligo. Studying a single subject over several years, they characterized the T-cell cytotoxic response to an antigen called Melan-A/MART-1 (Melanoma Antigen Recognized by T cells-1). Cytotoxic CD8 + T-cells recognize peptide antigens bound to MHC Class I molecules on target cells via the T-cell receptor (TCR), which is comprised of α- and β- chains. Each β-chain is composed of somatically rearranged V (variable), D (diversity), and J (joining) germline DNA segments that confer antigen specificity. Many recent studies have focused on the hypervariable D region of the β chain as the focal point of antigen recognition by the TCR. However, recent X-ray crystallography studies have revealed that TCR-α actually contacts the peptide antigen more extensively than does TCR-β, suggesting the possibility that peptide recognition may rely strongly on TCR-α, even though TCR-α does not contain a D region. In previous work (Mantovani *et al*, 2002) these authors found that HLA-A2-positive subjects markedly over-utilize a particular V region segment of the TCR α chain called AV2 in immature CD8 + thymocytes capable of recognizing Melan-A peptides. The same phenomenon was true of mature CD8 + cells in their vitiligo patient: 0.16% of all blood-derived CD8 + T-cells recognized a Melan-A peptide, as determined by binding of a tetrameric MHC-peptide complex. Twenty eight of 29 T-cell clones derived from this population expressed the AV2 TCR-α V region segment. In contrast, these T-cell clones expressed many different rearrangements of the TCR β chain. Melan-A-recognizing cells expressed the skin homing receptor CLA and displayed high avidity for the Melan-A antigen, suggesting that they had been selected for via repeated antigenic stimulation and could traffic to the skin. They were capable of killing normal melanocytes, and they persisted for more than three years in the patient's blood. Taken together, these data strongly suggest that these antigen-specific, AV2-restricted but polyclonal T-cells play an important role in at least some forms of vitiligo. Presumably, repeated exposure of AV2-bearing αβ-TCR to phagocytosed melanocytes leads to clonal expansion of many different T-cells recognizing various Melan-A-derived peptides. Even if a toxic process begins the chain of melanocyte destruction, it may be completed by a cytotoxic T-cell response. Thus, the neural hypothesis, the self-destruct hypothesis, and the autoimmune hypothesis need not be mutually exclusive.

Why should an entire family of TCRs characterized by the AV2 variable region segment recognize Melan-A? Interestingly, Melan-A displays strong homologies to certain microbial peptides, and it is likely that over evolutionary time, responses to microbes were critical in shaping the T-cell repertoire. Thus, similarities between bacterial and melanocyte peptides melanocytes may have played an evolutionary role in the emergence of vitiligo.

INNATE IMMUNE RESPONSES TO BACTERIAL DNA IN THE SKIN

Eukaryotic DNAs undergo enzymatic methylation of cytosine at CpG residues, and CpG dinucleotides are relatively uncommon in eukaryotes due to deamination of methyl-cytosine to thymidine. Methylation of DNA is correlated with inaccessibility of DNA in chromatin, and this methylation mechanism may have arisen as a silencing mechanism defense against genomic pathogens such as retroviruses. Bacteria and viruses lack this methylation mechanism and, as a consequence, are not deficient in CpG dinucleotides. Thus, this mechanism may have also have arisen as a way for eukaryotes to mount an immune response against non-self DNA. Bacterial and viral DNAs, and oligonucleotides containing CpG residues, are stimulatory to the normal human immune system and have been used as adjuvants for immunization, whereas immune responses to human DNA arise only in pathogenic states such as lupus erythematosus (LE). In this issue, Mölne, Collins, and Tarkowski (p. 294) injected DNA derived from the common skin pathogen Staphylococcus aureus into mice, and characterized the duration and composition of the resulting cutaneous infiltrate. They also compared these parameters after injection of synthetic CpG-containing oligonucleotides (20–24 nucleotides long) linked either by nuclease-sensitive phosphodiester bonds or nuclease-resistant phosphorothioate bonds. Staphylococcal DNA and phosphodiester oligos produced a brisk but short-lived inflammatory response, which peaked at two days and was characterized by a macrophage-rich infiltrate. Phosphorothioate oligos produced a slower and more pronounced response, which peaked at 7 days. The response was clearly dependent on the presence of CpG, as substitution of GpC for CpG in either type of oligonucleotide reduced the peak response by over 80%. By selective depletion of macrophages, polymorphonuclear leukocyte (PMNs), or T-cells in various ways, they showed that the clinical severity of the reaction was most strongly dependent on macrophages, followed by PMNs and T-cells. Given the rapidity of response and the relatively larger dependence on macrophages, this reaction has the hallmarks of an innate, rather than an acquired immune response. This would be

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consistent with recent observations that certain members of the Toll family of receptors recognize unmethylated CpG residues. These receptors have been strongly implicated in innate immunity via activation of NF-κB signaling. Other workers have shown that CpG oligonucleotides can serve as adjuvants in the skin, at least in part by accelerating the trafficking of Langerhans cells to draining lymph nodes and by encouraging a Th1 response. Thus, one can envision a day in the not-too-distant future in which CpG oligonucleotides might be tailored not only to boost immune Th1 immune responses in immunocompromised individuals, but also to deviate the immune response from Th2 to Th1 in conditions such as acute flares of Th2-mediated diseases such as atopic dermatitis, pemphigus, pemphigoid, and cutaneous lupus erythematosus. As "timing is everything" in the immune response, the ability to vary the duration of the innate immune response by altering the chemical structure of the oligos used may be an important means of fine-tuning cutaneous immunotherapy.

DUST MITES: HOW THEY GET CAN ON YOUR NERVES

Specific allergenic peptides derived from the house dust mite have been suggested to play a direct pathophysiological role in atopic dermatitis (AD), because many individuals display high levels of specific IgE directed against this ubiquitous ectoparasite. In this issue of the Journal, Huang *et al* (p. 289) develop an epicutaneous sensitization model of atopic dermatitis in Balb/c mice using Der p 8, a glutathione-S-transferase. Patches containing allergen or saline were applied three times for 4 days each, spaced 17 days apart. The animals developed a localized subacute dermatitis with both spongiosis and epidermal hyperplasia, along with infiltration of eosinophils, neutrophils, degranulated mast cells, CD4 and CD8 T-cells, and dendritic cells. Interestingly, there was also evidence of increased neurocutaneous inflammation, with ingrowth of nerve fibers making contact with mast cells and expressing CGRP and substance P. There was also evidence of a systemic Th2 response. As is the case in human AD, genetics may have played an important role in this model, as Balb/c mice are known to be biased towards Th2 responses in certain settings such as Leishmania infection. It would be interesting to know if the same allergen produces the same type of inflammation in other strains of mice. This is the first report of an AD-like rash after epicutaneous sensitization with a relevant human skin allergen, and it should be a valuable tool for cellular and genetic dissection of the complex neuro-immunopathogenesis of AD.

REFERENCES

Mantovani S, Palermo B, Garbellis, *et al*: Dominant TCR-alpha requirements for self antigen recognition in humans. *J Immunol* 169:6253–6260, 2002